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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/488,103	01/20/2000	Paul Stark	7453-0006-00	3945

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EXAMINER	
JOYNES, ROBERT M	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/488,103	STARK ET AL.	
	Examiner	Art Unit	
	Robert M. Joynes	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8,10-25,28-30,35,36 and 40-42* is/are pending in the application.

4a) Of the above claim(s) *2,9,26,27,31-34 and 37-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8,10-25,28-30,35,36 and 40-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Receipt is acknowledged of applicants' Amendment and Information Disclosure Statement filed on November 5, 2002 and applicants' Information Disclosure Statement on January 13, 2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-8, 10-25, 28-30- 35, 36 and 40-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites that the formulation comprises a pH-dependent dissolution profile and imparts a pH-dependent and pH-independent delay in bisoprolol release. It is unclear how a pH-dependent polymer can provide both a pH-dependent and pH-independent delay profile. Clarification is suggested. Upon review of the Amendment and the Specification, the Examiner is interpreting the claims as a formulation having a pH-independent dissolution profile. Dependent claims also recite that an ammonio methacrylic polymers is present in the formulation, which would lead to a pH-independent profile for the formulation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-6, 10-25, 28-30- 35, 36 and 40-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Noda et al. (US 5137733).

Noda teaches a controlled release pharmaceutical preparation comprising a core containing a medicinal compound and a coating layer containing a water-repellant salt and a water-insoluble and slightly water-permeable acrylic polymer having a trimethylammoniomethyl group (Col. 2, lines 3-8). An additional coating layer is added to the cores after the acrylic polymer layer (Col. 2, lines 32-39). The acrylic polymers are recited at Col. 2, lines 40-59. The additional coating layer is chosen from ethylcellulose or hydroxypropylcellulose (Col. 2, lines 60-66). The amount of coating layer is about 5% to about 80% based on the weight of the core (Col. 3, lines 11-21). The medicinal compound includes calcium antagonists, antiasthmatics, vitamins, antibiotics, antimalignant tumor agents, antipyretic analgesics and antihyperglycemic agents (Col. 3, lines 29-36). Various excipients are present in the core (Col. 3, lines 37-57). The acrylic coating layer further comprises plasticizers and coloring agents (Col. 4, lines 43-55). Example 12 recites the medicinal agent to be bisoprolol fumarate (Col. 9, lines 46-52).

Still further, Noda teaches formulations with differing number of coating layers (See Table 1 at Col. 6) wherein the lag time and complete dissolution are different. Preparation (b) exemplifies the dissolution profile of the instant claims as shown in Figure 1.

Therefore, Noda anticipated the limitations of the controlled release formulation of the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3-6, 10-25, 28-30- 35, 36 and 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noda et al. (US 5137733). The teachings of Noda are discussed above. While Noda teaches all of the limitations of the instant claims, the exact composition of the instant claims is not exemplified in the reference. The teachings of the reference as a whole are clearly suggestive of the limitations of the instant claims, namely a controlled release bisoprolol composition wherein the coating is an acrylic polymer that contains a methacrylate co-polymer.

Noda recites in the Specification that acrylic and methacrylic copolymers are suitable and preferred polymers for use in the composition. Noda also exemplifies

bisoprolol fumarate as a suitable medicinal agent for this controlled release system (See Example 12). Noda further teaches at the amount of acrylic coating depends on the size or form of the core but is generally about 5% to about 80% based in the weight of the core (Col. 3, lines 11-21).

Noda teaches that the system is designed to have an initial lag period before the medicinal agent is released or dissolved and that this initial period can be varied depending upon the number of layer of coating that are applied to the cores (Col. 5, lines 19-56). Further, the preparation can retain an effective blood concentration for many hours and can again differ with the amount of layers applied to the cores (Col. 5, lines 19-56). The preparation is suitable for once-a-day administration (Col. 6, lines 1-2).

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to prepare a controlled release system comprising bisoprolol fumarate in a core coated with an acrylic polymer wherein the coating polymer comprises an methacrylate polymer where an initial lag takes place after which the medicinal agent is released and maintained with an extended period of time (24 hours). The Noda reference is suggestive of the use of acrylic and methacrylic polymers as well as the incorporation of bisoprolol fumarate as the medicinal agent. Noda is also suggestive of varying the initial lag period and extended release times by varying the number of layers coated onto the cores. Noda provides guidance for determining what the initial lag times and dissolution rate would be for various coating layers (See Table 1, Col. 6 and Figure 1). It is within the skill of the art to vary the coating layers and

thereby adjust the initial lag period and dissolution profile for the system depending on the polymers used, the number layers applied and the medicinal agent to be administered.

One of ordinary skill in the art would have been motivated to do this to provide a controlled release pharmaceutical preparation giving a sigmoid type dissolution pattern wherein a lag time until the starting of the dissolution of a medicinal compound and the rate of the following dissolution can be controlled and the rate of dissolution does not depend on the pH of a medium for the dissolution.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noda et al. in combination with Oshlack et al. (US 5580578). The teachings of Noda are discussed above. Noda does not expressly teach that a barrier layer is incorporated between the core and the acrylic polymer layer.

Oshlack teaches the incorporation of a barrier layer between the medicinal core and the acrylic coating layer (Col. 13, line 62 – Col. 14, line 2). The barrier layer can be hydroxypropyl methylcellulose or any film-forming agent known in the art (Col. 13, line 62 – Col. 14, line 2). The barrier layer is used to separate the medicinal agent from the acrylic polymer coating (Col. 13, line 62 – Col. 14, line 2).

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to incorporate a barrier layer between the medicinal core and the acrylic polymer layer.

One of ordinary skill in the art would have been motivated to do this to separate the medicinal agent from the acrylic polymer coating.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1, 3-6, 10-25, 28-30- 35, 36 and 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noda in view of The Handbook for Pharmaceutical Excipients, Second Edition, *Polymethacrylates*, pp. 362-66, 1994. The teachings of Noda are discussed above. Noda does not expressly teach all methacrylates that are suitable for coating compositions.

The Handbook of Pharmaceutical Excipients teaches the various forms of methacrylic polymers suitable for coating pharmaceutical formulations. The Handbook shows both pH-dependent and pH-independent polymers that are suitable for coating preparations that delay or sustain the release of the drug from the formulation.

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to prepare a pharmaceutical formulation that is coated with a methacrylic polymer suitable for coatings pharmaceutical formulations wherein the release of the drug is delayed and/or sustained.

One of ordinary skill in the art would have been motivated to choose a suitable methacrylic polymer to prepare a formulation that achieves the same dissolution profile of delaying the release of the drug from the formulation and thereafter sustaining the release of the drug with the same expected results.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noda et al. in combination with The Handbook of Pharmaceutical Excipients in further combination with Oshlack et al. (US 5580578). The teachings of Noda and the Handbook are discussed above. Noda does not expressly teach that a barrier layer is incorporated between the core and the acrylic polymer layer.

Oshlack teaches the incorporation of a barrier layer between the medicinal core and the acrylic coating layer (Col. 13, line 62 – Col. 14, line 2). The barrier layer can be hydroxypropyl methylcellulose or any film-forming agent known in the art (Col. 13, line 62 – Col. 14, line 2). The barrier layer is used to separate the medicinal agent from the acrylic polymer coating (Col. 13, line 62 – Col. 14, line 2).

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to incorporate a barrier layer between the medicinal core and the acrylic polymer layer.

One of ordinary skill in the art would have been motivated to do this to separate the medicinal agent from the acrylic polymer coating.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments filed February 26, 2003 have been fully considered but they are not persuasive. Applicants argue that the prior art fails to teach a pH-

dependent polymer for the coating of the formulation that imparts a pH-dependent and pH-independent delay for the drug. As stated above, it is the position of the Examiner that the claims are interpreted as formulations that are pH-independent for two reasons: 1) Claim 1 is unclear as to how a polymer that is pH-dependent can impart both a pH-dependent and pH- independent delay profile; and 2) dependent claims recite that the polymer is an ammonio methacrylate polymer, which would make the polymer pH-independent as previously claimed and as taught in the prior art.

Working from that interpretation, the prior art rejections are maintained. The prior art teaches a formulation that has the same release profile as the instant claims. Bisoprolol is the active agent and is coated with an acrylic polymer that delays the release and then provides a sustained release profile. The Examiner sees no criticality in defining the polymer as pH-dependent when the same profile is achieved.

The Examiner adds a rejection in this Office Action due to the amendment that takes into consideration the possibility that applicants can show a pH-dependent polymer that does impart both a pH-dependent and pH-independent delay for the drug. Working under the assumption that the polymer is pH-dependent, the secondary reference was added to show that various acrylic and/or methacrylic polymers exist. Further, these polymers are known to be pH-dependent or pH-independent and are used as coatings and binders for pharmaceutical preparations. It is the position of the Examiner that one of ordinary skill in the art would be able to select a polymer that suitable for such formulations that imparts a delayed release followed by a sustained release of the drug. The prior art teaches such a profile and suggests particular

polymers to do so. The prior art even gives guidance to vary the delayed release by varying the polymer used and the number of layers of the polymer applied. The secondary reference shows that the polymers of the primary reference are similar or equal to those that are also listed in the Handbook. No criticality is seen in the particular recitation of only pH-dependent polymers. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use a polymer from the Handbook in the compositions of Noda for its art intended purpose. The selection of a known material based on its suitability for its intended use is obvious absent a clear showing of unexpected results attributable to the applicants' specific selection.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Joynes whose telephone number is (703) 308-8869. The examiner can normally be reached on Mon.-Thurs. 8:30 - 6:00, alternate Fri. 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on (703) 308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3592 for regular communications and (703) 305-3592 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Robert M. Joynes
Patent Examiner
Art Unit 1615
May 14, 2003

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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